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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,207	10/27/2003	Ekambar R. Kandimalla	HYB-005US7	3842

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
10/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/694,207	KANDIMALLA ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,28,29,34 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26, 28-29 and 34-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 31 July 2008 has been entered.

2. Claims 1-25, 27, 30-33 and 36-70 are cancelled.
Claims 26 and 34 have been amended.

3. Claims 26, 28-29 and 34-35 are under consideration.

Objections/Rejections Withdrawn

4. The objection to the specification as failing to provide proper antecedent basis for the claimed subject matter, e.g., immunostimulatory dinucleotide of formula C*pG*, is withdrawn in view of the cancellation of claim 55.

5. the rejection of claims 55, 57-58 and 66-67 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the cancellation of the claims.

Rejections Maintained

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The rejection of claims 26, 28-29 and 34-35 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claims

contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 7/31/2008 states that the claimed oligonucleotides are limited to those containing an immunostimulatory dinucleotide C*pG, wherein C* is a non-natural pyrimidine nucleoside selected from the group consisting of 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil. Applicant states that the PTO has already decided that these oligonucleotides meet the written description requirement as evidence by the issuance of US Patent 7,262,286 having the identical specification, where the only difference is that instant claim 26 recites that the immunostimulatory oligonucleotides elicit an immune response. Further, applicant asserts that the rejection incorrectly states that the ability to elicit an immune response is demonstrated for only a single species and applicant points to Figures 23, 24 and 26, which show that the claimed oligonucleotide compounds wherein C* is 5-hydroxycytosine, 5-hydroxymethylcytosine or 4-thiouracil are all immunostimulatory. Applicant states that the Office Action shows no reason to doubt the ability of the fourth member of the Markush group, wherein C* is N4-alkylcytosine, to be immunostimulatory. Applicant concludes that claims 26 and 28-29 satisfy the written description requirement. Applicants' arguments have been fully considered but are not found persuasive. Applicants' remarks regarding US Patent 7,262,286 are acknowledged, however, applicant is reminded that each application is examined on its own merits and the examiner is precluded from comment on US Patent 7,262,286 under 35 U.S.C. 282. See MPEP 1701. Further, as noted by applicant the instant claims require an activity, i.e., elicit an immune response, and as discussed in more detail below, the instant application does not provide a correlation between the common structure C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil and a common function, i.e., generate an immune response in a patient or treat caner in a patient. With respect to the scope of the claims and as set forth in the previous Office Action (mailed 3/31/08), the claims are directed to methods of generating an immune response or treating

cancer in a patient comprising administering an immunostimulatory oligonucleotide compound comprising an immunostimulatory dinucleotide of formula C*pG, wherein C* is a non-natural pyrimidine nucleoside selected from the group consisting of 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil, and G is guanosine. Thus, while the claims are drawn to the therapeutic administration of immunostimulatory oligonucleotides containing an immunostimulatory dinucleotide C*pG, wherein C* is a non-natural pyrimidine nucleoside selected from the group consisting of 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil, the issue remains that the claims encompass thousands or millions of immunostimulatory oliognucleotides that differ in length and sequence, inclusive to a variety of subgenera having disparate structures and functions. Further, applicants' reference to Figures 23, 24 and 26 and arguments are curious given that the Figures demonstrate only a single immunostimulatory oligonucleotide sequence (5'-CTATCTGACGTTCTCTGT-3') (i.e., a single species of immunostimulatory oligonucleotide) comprising the immunostimulatory dinucleotide C*pG, wherein C* is a non-natural pyrimidine nucleoside selected from the group consisting of 5-hydroxycytosine, 5-hydroxymethylcytosine or 4-thiouracil. The issue remains the genus of immunostimulatory oligonucleotide sequences comprising the recited non-natural pyrimidine nucleosides, not that the fourth member of the Markush group, wherein C* is N4-alkylcytosine would not be immunostimulatory.

For convenience. It is reiterated that the written description of the present application only sets forth a single immunostimulatory oligonucleotide (i.e., 5'-CTATCTGACGTTCTCTGT-3') comprising the formula C*pG, wherein C* is 5-hydroxycytosine, 5-hydroxymethylcytosine or N4-ethylcytosine that stimulates an immune response, however, the claims encompass thousands or millions of immunostimulatory oligonucleotides that differ in length and sequence, and which generate an immune response in a patient or treat cancer in a patient. The structures of the immunostimulatory oligonucleotides comprising the formula C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil that generate an immune response in a patient or treat caner in a patient are

not known and the genus is inclusive to a variety of subgenera having disparate structures and functions. Thus, the instant disclosure does not provide sufficient written description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus or various subgenera of immunostimulatory oligonucleotides comprising the formula C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil that generate an immune response in a patient or treat caner in a patient. See *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406. For example, Figures 22, 23 and 26 as pointed to by applicant demonstrate that the immunostimulatory oligonucleotide 5'-CTATCTGACGTTCTCTGT-3' in the absence of C* elicits an immune response that is equal to or greater than the immune response elicited when C* is present and selected from 5-hydroxycytosine, 5-hydroxymethylcytosine and 4-thiouracil. The instant application does not provide a correlation between the common structure C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil and a common function, i.e., generate an immune response in a patient or treat caner in a patient. Again, the specification discloses that a CpG oligonucleotide comprising the cytosine analogs, particularly 5-hydroxycytosine or N4-ethylcytosine, can be modulated significantly by incorporating appropriate chemical modifications in the 5'-flanking sequence, suggesting that these cytosine analogs in a CpG-motif are recognized as part of an immunostimulatory motif. The specification also discloses that when the cytosine of the CpG-motif is replaced with uracil, no immunostimulatory activity was observed. Similarly, the relevant CpG immunostimulatory oligonucleotide art teaches that the length, sequence and backbone modification can alter the immunostimulatory properties of CpG oligonucleotides. Vollmer et al (Antisense and Nucleic Acid Drug Development, 12:165-175, 2002, cited on PTO-892 mailed 3/31/08) teach that both thymidine content and length of thymidine

stretches affect CpG-mediated immunostimulation and oligonucleotides with methylated CpG motifs have length-dependent immunostimulatory effects (e.g., see pg. 173 and Figs. 2-4). Vollmer et al also discloses that poly-G sequences have independent immune effects and can modulate the activity of CpG motifs in either an agonistic or antagonistic fashion (see pg. 166 2nd col.). Verthelyi et al (The Journal of Immunology, 168:1659-1663, 2002, cited on PTO-892 mailed 8/6/07) states that "[D]ue to evolutionary divergence in CpG recognition between species, ODN that are highly active in rodents are poorly immunostimulatory in primates, and vice versa" (e.g., pg. 1659, left col.) and "CpG ODN that activate human immune cells in vitro are only weakly immunostimulatory in mice" (e.g., pg. 1662, Discussion, first par.). Dittmer et al (Current Opinion in Microbiology, 6:472-477, 2003, cited on PTO-892 mailed 8/6/07) reports that "[U]nfortunately, CpG-ODN that optimally stimulate mouse cells were only weakly effective in human cells, thus they could not be used for the treatment of humans" (e.g., pg. 472, right col., bottom par.). Thus, one of skill in the art could not predict the operability of any other species of immunostimulatory oligonucleotides comprising an immunostimulatory dinucleotide having the formula C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil other than those disclosed. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]. " See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed."

Further, it is not sufficient to define a substance solely by its principal biological property, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function". Similarly, the function of eliciting an immune response or being "immunostimulatory" does not distinguish any immunostimulatory oligonucleotide having the formula C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil from others having the same activity or function and as such, fails to satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of genus of immunostimulatory oligonucleotides comprising the formula C*pG, or the various subgenera of immunostimulatory oligonucleotides comprising the formula C*pG, wherein C* is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil that generate an immune response in a patient or treat caner in a patient, and therefore conception is not

achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

For these reasons and those already of record, the rejection is maintained.

8. No claim is allowed.

9. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643